REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application are respectfully requested.

Claim 1 has been amended relating to matters of form, *i.e.*, "carboxylic acid" has been replaced with the chemical formula "COOH," and letters have been used to separate the various substituents of the formula, *e.g.*, (a)-(k) was used for R^1. Tetrahydroquinoline and benzoxazine have been inserted to more clearly define the fused heterocyclic ring for R^1 and R^2 when the ring A is benzene ring. Support for this amendment may be found, at the very least, at page 9, lines 26-35. Claim 1 has also been amended to recite that when A is a benzene ring and R^1 is an amino group, R^2 and R^3 are not a hydrogen atom at the same time. Support for this amendment is provided in the compounds of the Examples. No new matter is added by these amendments.

Applicants affirm the election of the Group I invention, claims 1-6 and 13-24.

Regarding the Examiner's objection to the missing of page 45 and the use of pages 43/1, and 46/1 pointed out in paragraph 2 of the Office Action, applicants note that page 45 is not missing from the application as filed. The application as filed has pages 1-49. An Article 34 Amendment was filed, which contained new pages 42, 43, 43/1, 44, 46, 46/1 and 48 were filed. Since page 45 was not being amended, it was not submitted with the Article 34 Amendment. Moreover, the use of 43/1 and 46/1 was used to designate where the amended pages were longer than the original pages and a second page was necessary. This designation is commonly used for PCT filings. However, by this amendment, applicants have enclosed an additional copy of pages 45 and 47, which were

not included with the Article 34 Amendment, and are requesting that the pages be renumbered in sequential order.

The Abstract was objected to as allegedly being defective. The Abstract has been amended in part as helpfully suggested by the Examiner to recite treatment of specific diseases. Applicants note that if the A and R^1 substituents are defined as requested, the Abstract would be longer than the allowed 150 word limit. The definition of A has thus been added, but additional substituents such as R^1 have not been defined therein. Any suggestions for additional amendments to the Abstract would be appreciated.

Claims 1-6 have been rejected under the judicially created doctrine of obviousness-type double patenting. This rejection is respectfully traversed.

The definition for "R^1 and R^2 are C_1-C_4 lower alkyl which may be substituted by a carboxyl group" is not present in claim 8 of US '631. The definition of R^1 and R^2 in claim 8 of US '631 reads as follows:

R^1 and R^2 are the same or different and represent

a hydrogen atom,

a halogen atom,

a C_1 to C_4 lower alkyl group which may be substituted with a halogen atom,

...

a tetrazolyl group,

a carboxyl group which may be esterified with a C_1 to C_4 lower alkyl group or an allyl group, or

a C_1 to C_4 lower alkoxy group ...

Claim 8 of the '631 Patent thus does not recite that R^1 is a C_1 to C_4 lower alkyl that is substituted by a carboxyl group, as alleged in the Official Action. Instead, in claim 8, R^1 and/or R^2 may be "a C_1 to C_4 lower alkyl group which may be substituted with a halogen atom," or R^1 and R^2 may be "a carboxyl group which may be esterified with a C_1 to C_4 lower alkyl group or an allyl group."

In view of the above, withdrawal of the obviousness-type double patenting rejection is respectfully requested and believed to be in order.

Claims 1-6 have also been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Fukami et al, U.S. Patent No. 5,814,631. In column 52, example 148, the '631 Patent is cited for teaching the synthesis of 3-(4-aminobenzenesulfonyl)-7-chloro-2,4(1H,3H)-quinazolindone. This rejection is respectfully traversed.

According to the Official Action, the compound of example 148 of the '631 Patent is allegedly the same as applicants except that it is excluded by the proviso. Moreover, it is asserted that (1) the compounds are position isomers; (2) the substituents on the A ring are floating (e.g., formula I); and (3) the reference teaches substituents on the 2 or 3 positions (e.g., example 127, column 48). Position isomers are said to be structurally obvious in view of each other, and would be expected to have the same properties. These assertions, however, are in error. The compound of example 148 differs from those encompassed by applicants' claims 1-6 in additional ways.

For example, as shown in the non-executed Rule 132 Declaration submitted herewith, the solubilities in water of the compounds encompassed by the instant claims, for example, the compounds described in Examples 13, 17 and 18 of the present application,

are remarkably or unexpectedly high than that of Example 148 of US '631. The results can be summarized as follows:

Table I

Sample Compound	Solubility in Water (μg/mL)
Example 13	88.5
Example 17	78.9
Example 18	98.8
Example 148 of US '631	6.9

Namely, when compared with the cited compound of example 148 having 4-aminobenzenesulfonyl, the compounds having NH_2 for R^1 and the substituents for R^2 and R^3 (i.e., the present compounds 17 and 18) and the compound having NHCOR for R^1 (i.e., the present compound 13) have unexpectedly high solubilities in water because of the position isomer. Since one skilled in the art would have expected the position isomers to have the same properties, the properties of the claimed compounds are truly unexpected.

As is well-known in the art, the oral absorbability in the oral administration depends upon the dissolving rate of the drug and the dissolving rate in the case of oral administration generally depends upon the solubility in water of the drug.

Thus, the solubilities of the present compounds 13, 17 and 18 are remarkably higher than that of the cited compound 148. Because of the difference in solubilities, when compared with the cited compound of example 148, the compounds of the instant invention encompassed by claims 1-6 are expected to have a higher oral absorbability and bioavailability than those of the '631 Patent. The instantly claimed compounds would thus

be expected to have a higher effectiveness when orally administration. In addition, in the case of non-oral administration, since drugs should be dissolved in injection solutions, the drugs having a solubility in water are advantageous for non-oral administration as well.

In view of the marked difference in properties of the compound of example 148 of the '631 Patent and the compounds of claims 1-6 of the instant invention, the claims of the instant invention would not be obvious in view of the '631 Patent.

Moreover, unexpected results are obtained by the instant invention, as evidenced by the §132 Declaration. One skilled in the art would not have expected such a marked increase in solubility in water of the claimed position isomers. This increase in solubility has many beneficial effects in terms of the use of such compounds in pharmaceutical compositions.

In view of the above, the present invention is not obvious in view of the '631 Patent. Withdrawal of this rejection is respectfully requested and believed to be in order.

Claims 1-6 and 13-24 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly not being described by the specification. This rejection is respectfully traversed.

Withdrawal of this rejection is respectfully requested and believed to be in order.

Claims 14-17 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not enabled by the specification. This rejection is rendered moot by the instant amendment.

According to the Official Action, the specification does not teach how to prevent the claimed diseases. In order to expedite prosecution of this application, the claims have been amended to recite methods for treatment of the recited diseases. Applicants reserve the right to file a continuation application directed to methods for prevention.

Withdrawal of this rejection is respectfully requested and believed to be in order.

Claim 17 has been rejected under 35 U.S.C. §112, first paragraph, as allegedly the specification does not enable non-diabetic renal disorders. This rejection is respectfully traversed.

This phrase is said to be very broad and encompass every renal disorder except diabetes. One skilled in the art would recognize that the claim as written is fully enabled. The present specification does enable treatment of non-diabetic disorders. The terminology of "diabetic and non-diabetic renal diseases" has been quite popular and is commonly used in many scientific papers (*e.g., Kidney Int Suppl.*, Vol 58:S66, 1997; *Adv Perit Dial*, Vol. 9:156, 1993).

Moreover, one skilled in the art would recognize that renal system disorders in general could be treated by the instant invention, in contradistinction to the assertions at pages 8-9 of the Official Action. It is noted that angiotensin II has been thought to participate in the pathogenesis of both diabetic and non-diabetic diseases. For example, it has been reported that inhibitors for angiotensin-converting enzyme (ACE) reduce proteinuria and slow disease progression to end-stage renal failure safely and more

effectively than non-angiotensin-converting enzyme therapy (*Curr Opin Nephrol Hypertens*, Vol. 6:489, 1997). ACE inhibitors delay the onset and slow the progression of diabetic nephropathy as well (*Ann Pharmacother*, Vol. 27:344, 1993). Moreover, it has been shown that an angiotensin II receptor blocker, losartan, decreases albumin excretion in hypertensive patients with non-diabetic nephropathy (*Nephrol Dial Transplant*, Vol. 13:3096, 1998).

Chymase, on the other hand, has an ability to convert angiotensin I to angiotensin II, which may be more significant than ACE in humans (see "BACKGROUND ART" in the present patent, and *J Biol Chem*, Vol. 265, 22348, 1990). In view of the above, one skilled in the art would recognize that the chymase inhibitors of the instant invention could be used for the treatment of a variety of renal disorders, both diabetic and non-diabetic.

Claims 1-6 and 13-24 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is believed to be rendered moot by the instant amendment. Withdrawal of the rejection is respectfully requested and believed to be in order.

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (508) 339-3684 so that prosecution of the application may be expedited.

Respectfully submitted,

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Page 4, Paragraph Beginning at Line 10

R^1 represents a hydroxyl group, an amino group, a C_1 to C_4 lower alkylamino group which may be substituted with a carboxylic acid group, a C_7 and C_{10} lower aralkylamino group which may be substituted with a carboxylic acid group, an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a carboxylic acid group, an amino group acylated with an aromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a carboxylic acid group, a C_1 to C_4 lower alkyl group substituted with a carboxylic acid group, or a C_2 to C_4 lower alkenyl [alkylene] group which may be substituted with a carboxylic acid group.

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Page 7, Paragraph Beginning at Line 23

Preferable examples of the C_2 to C_4 lower [alkylene] alkenyl group substituted with a carboxylic acid group represented by R^1 are an acrylic acid group, a crotonic acid group, etc.

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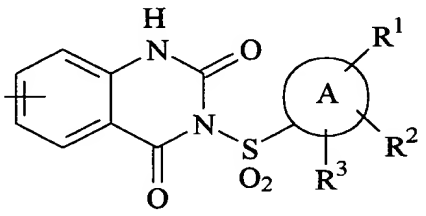
Marked-up Claims 1-3, 6, and 14-17

1. (Amended) A quinazoline derivative having the following formula (1) and a pharmaceutically acceptable salt thereof:



(1)

wherein the ring A represents an aryl group:

R^1 represents (a) hydroxyl group, (b) an amino group, (c) a C_1 to C_4 lower alkylamino group which may be substituted with a COOH [carboxylic acid] group, (d) a C_7 and C_{10} lower aralkylamino group which may be substituted with a COOH [carboxylic acid] group, (e) an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a COOH [carboxylic acid] group, (e) an amino group acylated with an aromatic ring carboxylic acid which may be substituted with a COOH [carboxylic acid] group, (g) an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a COOH [carboxylic acid] group, (h) an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a COOH [carboxylic acid] group, (i) an amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a COOH [carboxylic acid] group, (j) an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a COOH [carboxylic

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Marked-up Claims 1-3, 6, and 14-17

acid] group, (k) a C_1 to C_4 lower alkyl group substituted with a COOH [carboxylic acid] group, or (l) a C_2 to C_4 lower alkenyl [alkylene] group which may be substituted with a COOH [carboxylic acid] group;

R^2 and R^3 may be the same or different and represent (a) a hydrogen atom, (b) an unsubstituted or substituted C_1 to C_4 lower alkyl group, (c) a halogen atom, (d) a hydroxyl group, (e) a C_1 to C_4 lower alkoxyl group, (f) an amino group, (g) an unsubstituted or substituted C_1 to C_4 lower alkylamino group, (h) an unsubstituted or substituted C_1 to C_{10} aralkylamino group, (i) an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a COOH [carboxylic acid] group, (j) an amino group acylated with an aromatic ring carboxylic acid which may be substituted with a COOH [carboxylic acid] group, (k) an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a COOH [carboxylic acid] group, (l) an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a COOH [carboxylic acid] group, (m) an amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a COOH [carboxylic acid] group, (n) an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a COOH [carboxylic acid] group, or (o) a COOH [carboxylic acid] group or

when the ring A is benzene ring, R^1 and R^2 may form, together with the substituting benzene ring, (a) a tetrahydroquinoline ring or (b) a benzoxazine ring [fused heterocyclic ring] which may be substituted with a COOH [carboxylic acid] group and in which the

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Marked-up Claims 1-3, 6, and 14-17

carbon atom in the ring may form a carbonyl group and R^3 is the same as defined above; and

X represents (a) a hydrogen atom, (b) a C_1 to C_4 lower alkyl group, (c) a C1 to C_4 lower alkoxy group, (d) a halogen atom, (e) a hydroxyl group, (e) an amino group, or (g) a nitro group, with the proviso that, when [the ring] A is a benzene ring and R^1 is an amino group, [and both] ~~R^2 and R^3~~ are not a hydrogen atom at the same time [, R^1 is not positioned at the para-position to the sulfonyl group].

2. (Amended) A quinazoline derivative or a pharmaceutically acceptable salt thereof as claimed in claim 1, wherein, in the formula (1), R^1 is a hydroxyl group, an amino group, a C_1 to C_4 lower alkylamino group substituted with a COOH [carboxylic acid] group, or an amino group acylated with a C_1 to C_4 lower aliphatic acid substituted with a COOH [carboxylic acid] group.

3. (Twice Amended) A quinazoline derivative or a pharmaceutically acceptable salt thereof as claimed in claim 1, wherein, in the formula (1), R^2 is a [carboxylic acid] COOH group or a hydrogen atom.

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Marked-up Claims 1-3, 6, and 14-17

6. (Twice Amended) A chymase inhibitor having as an effective ingredient a quinazoline derivative or its pharmaceutically salt according to claim 1, and a pharmaceutically acceptable carrier therefor.

14. (Amended) A method for [prevention or] treatment of allergic diseases or rheumatic diseases comprising administering to a patient in need of such prevention or treatment an effective amount of a quinazoline derivative or salt thereof according to claim 1.

15. (Amended) A method for [prevention or] treatment of bronchial asthma, eczema, atopic dermatitis, mastocytosis, scleriasis or rheumatoid arthritis comprising administering to a patient in need of such prevention or treatment an effective amount of a quinazoline derivative or salt thereof according to claim 1.

16. (Amended) A method for [prevention or] treatment of cardiac and circulatory system diseases due to the abnormal exacerbation of Angiotensin II production comprising administering to a patient in need of such prevention or treatment an effective amount of a quinazoline derivative or salt thereof according to claim 1.

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Marked-up Claims 1-3, 6, and 14-17

17. (Amended) A method for [prevention or] treatment of cardiac insufficiency, hypercardia, stasis cardiac diseases, hypertension, arteriosclerosis, peripheral circulatory diseases, revasoconstriction after PTCA, diabetic renal disorders or non-diabetic renal disorders, coronary diseases including cardiac infarction, angioendothelia or vascular disorders accompanying arterialization and atheroma comprising administering to a patient in need of such prevention or treatment an effective amount of a quinazoline derivative or salt thereof according to claim 1.